

EXHIBIT -2



**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**MEMORANDUM**

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DATE: 26 March 2002

FROM: Charles E. Lee, MD  
Medical Officer, Division of Pulmonary and Allergy Drug Products

THROUGH: Robert J. Meyer, MD  
Director, Division of Pulmonary and Allergy Drug Products

SUBJECT: Background for the Nonprescription Drugs Advisory Committee meeting  
on the proposed over-the-counter switch of the chronic idiopathic  
urticaria indication of loratadine

TO: Members of the Nonprescription Drugs Advisory Committee, selected  
members of the Pulmonary-Allergy Drugs Advisory Committee, and  
invited consultants

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**BACKGROUND**

Loratadine is currently approved and available under prescription in the U.S. for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age and older. Schering-Plough has submitted an application to switch loratadine (Claritin®) from prescription status to over-the-counter (OTC) status for the relief of symptoms of allergic rhinitis and chronic idiopathic urticaria (CIU) in consumers 6 years of age and older. The proposed indications for OTC use are "hay fever and other respiratory allergies," and "itching and rash due to recurring or chronic hives of an unknown source."

The intention of this advisory committee meeting is to discuss the applicant's proposal to market loratadine for the CIU indication in an OTC setting. In the applicant's opinion, the available data support OTC use of loratadine for both allergic rhinitis and CIU indications. The proposed switch for the CIU indication applies to the three single ingredient loratadine products, 10-mg tablets, 10-mg Reditabs, and 1-mg/mL syrup.

Loratadine has a relatively long marketing history in the U.S. and elsewhere in the world. Loratadine was introduced to the world market as a prescription product in Belgium in 1988, and was approved in

the U.S. as a prescription drug for seasonal allergic rhinitis in April 1993 and for CIU in September 1995. Loratadine was first introduced as a non-prescription product in Canada in 1990. In most countries where loratadine is available as a non-prescription product, it is indicated for allergic rhinitis, allergic skin disorders, and hives. However, in most of these countries, loratadine is marketed "behind-the-counter" (i.e., dispensed by a pharmacist without a prescription). In some countries, including the United Kingdom, Canada, and Australia, loratadine is available OTC (i.e., purchased without pharmacist intervention).

The Food, Drug, and Cosmetic Act restricts a drug to prescription status if "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drugs." This has been interpreted to mean that a drug should be restricted to prescription use if intervention of a learned intermediary is required for its proper use (administration and monitoring), otherwise the drug is to be marketed OTC. Hence, a key issue in determining the appropriateness of a drug product for OTC marketing is its intended use or indication.

Allergic rhinitis is a condition for which OTC use of antihistamines has been determined to be appropriate. There are currently antihistamines whose usage is guided by OTC monograph labeling (21 CFR 341.72), such as chlorpheniramine and brompheniramine, which were classified as generally recognized as safe and effective (GRAS/E) in the OTC Drug Review. The OTC Drug Review recommended that other antihistamines, such as diphenhydramine, be switched from prescription to OTC status for this indication. Clemastine was approved as an OTC product by a direct switch from a prescription NDA product. For each of these antihistamines, the indication for which OTC status has been afforded has been relief of various symptoms due to hay fever, or other respiratory allergies (allergic rhinitis). Currently there are no OTC antihistamines marketed in the U.S. for either CIU or acute urticaria.

On July 6, 1998, Blue Cross of California (now WellPoint Health Networks) initiated Citizen's Petition 98P-0610/CP, which requested that the Agency switch three newer, relatively non-sedating antihistamines to OTC status. The three antihistamines were cetirizine, fexofenadine, and loratadine. This issue was discussed at a combined meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on May 11, 2001. The focus of that discussion was the allergic rhinitis indication. The majority opinion of the advisory committee was that these three newer antihistamines may be used appropriately and safely for allergic rhinitis by consumers without intervention by a learned intermediary. The committee vote was supportive of OTC marketing status of these drugs for the allergic rhinitis indication. Therefore, the efficacy and safety of these drugs for allergic rhinitis in an OTC setting is not a question for discussion for this meeting. The CIU indication was not discussed at the May 11, 2001 advisory committee meeting, however.

Cardinal features of urticaria are cutaneous wheals associated with redness and itching. CIU is defined as the daily or almost daily occurrence of these wheals for at least 6 weeks. The clinical diagnosis of CIU is made by excluding other forms of chronic urticaria, such as the physical urticarias, which include

dermatographism and cold urticaria, and urticarial vasculitis.<sup>1</sup> Recently, some patients with CIU have been recognized to have an autoimmune condition associated with circulating antibodies directed against the IgE receptor or against IgE.<sup>1, 2</sup> Nonpharmacologic treatment measures for patients with chronic urticaria of various forms include avoidance of aggravating factors such as overheating and alcohol use.<sup>1</sup> Antihistamines form the foundation for pharmacologic treatment of chronic urticaria.<sup>1, 2</sup> The Medical Officer review of an NDA most recently submitted to the Agency in support of a CIU indication for a new antihistamine is included with this backgrounder.<sup>3</sup> The review is included as an example only of a clinical program conducted to support the CIU indication for a typical antihistamine. This specific NDA is for desloratadine, which is a metabolite of loratadine. The clinical programs that supported the CIU indication for cetirizine, fexofenadine, and loratadine were generally similar in scope to the desloratadine program that has been included in this package.

Medications that are currently marketed in the U.S. for treatment of urticaria are exclusively prescription products. As noted above, there currently are no OTC products approved in the U.S. for the treatment of CIU, urticaria of other forms, or itching due to hives. Neither are CIU, urticaria, or itching due to hives recognized as OTC monograph indications. Prescription products approved for chronic urticaria, CIU, or manifestations of chronic urticaria include cetirizine, desloratadine, fexofenadine, hydroxyzine, and loratadine. Products marketed for the relief of manifestations of urticaria include cyproheptadine, hydroxyzine, promethazine, and a chlorpheniramine/phenylephrine/methscopolamine combination. The CIU indication has been granted based on the demonstration of efficacy and safety in adequate and well-controlled studies. Examples of drugs that have been approved in this manner include cetirizine, desloratadine, fexofenadine, and loratadine. As loratadine has been studied in the treatment of CIU in the prescription setting, its efficacy and safety under these circumstances is not in question, and is not a subject for discussion at this meeting.

There are several subjects for discussion at this meeting, the broadest of which is the appropriateness of urticaria as an OTC indication. A more specific subject for discussion is the scientific basis for granting such an indication, if urticaria is determined to be an appropriate OTC indication. The final and most specific subject for discussion relates to the circumstances, if any, under which loratadine should be labeled for any or all of these indications. It is important to recognize that approval of such a product for treatment of urticaria in an OTC setting would impact not only the intended population of patients with CIU, but would also be likely to impact patients who have other conditions in which efficacy and safety has not been studied. These other conditions might include, among others, acute urticaria, various conditions misidentified by the patient as urticaria, and any other conditions that may result in itching and rash of the skin, as long as its source is unknown, as the OTC label would propose.

#### **ATTACHMENTS**

1. Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000;105:664-72.
2. Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002;346:175-9.
3. Medical Officer Review, NDA 21-297, 6/15/01.